

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

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| Applicant's or agent's file reference Case 21704 WO | FOR FURTHER ACTION | |
| See Form PCT/IPEA/416 | | |
| International application No. PCT/EP2004/003109 | International filing date (day/month/year) 24.03.2004 | Priority date (day/month/year) 04.04.2003 |
| International Patent Classification (IPC) or national classification and IPC C07C233/47, C07C231/02, C07C231/14 | | |
| Applicant DSM IP ASSETS B.V. et al. | | |
| <p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> <i>sent to the applicant and to the International Bureau</i> a total of 2 sheets, as follows:</p> <ul style="list-style-type: none"> <input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. <p>b. <input type="checkbox"/> <i>(sent to the International Bureau only)</i> a total of (indicate type and number of electronic carrier(s)), containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p> | | |
| <p>4. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Box No. I Basis of the opinion <input type="checkbox"/> Box No. II Priority <input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement <input type="checkbox"/> Box No. VI Certain documents cited <input checked="" type="checkbox"/> Box No. VII Certain defects in the international application <input type="checkbox"/> Box No. VIII Certain observations on the international application | | |
| Date of submission of the demand 06.10.2004 | Date of completion of this report 07.03.2005 | |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Goetz, G Telephone No. +49 89 2399-8105 | |
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**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/003109

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
 - international search (under Rules 12.3 and 23.1(b))
 - publication of the international application (under Rule 12.4)
 - international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-14 as originally filed

Claims, Numbers

1-10 received on 25.09.2004 with letter of 22.09.2004

- a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
- 3. The amendments have resulted in the cancellation of:
 - the description, pages
 - the claims, Nos.
 - the drawings, sheets/figs
 - the sequence listing (*specify*):
 - any table(s) related to sequence listing (*specify*):
- 4. This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - the description, pages
 - the claims, Nos.
 - the drawings, sheets/figs
 - the sequence listing (*specify*):
 - any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/003109

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|--------------------|
| Novelty (N) | Yes: Claims | 1-14 ¹⁰ |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | 1-18 ⁹ |
| | No: Claims | 10 |
| Industrial applicability (IA) | Yes: Claims | 1-14 ¹⁰ |
| | No: Claims | |

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

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REPORT ON PATENTABILITY
(SEPARATE SHEET)International application No.
PCT/EP2004/003109

D1 DE-A-2004099
D2 US-A-3646061

I. Present claims 1 to 8 are in particular characterized by the fact that the reaction of alanine with a dialkyl oxalate under non-acidic conditions is carried out without the presence of an added base or an added alkanol.

Such a process is neither disclosed in D1 nor in D2:

D2 can be considered as the closest prior art document since it discloses the preparation of the same product. The process of D2 differs from the presently claimed one by the fact that alanine is reacted with the oxalic acid in the presence of an alkanol. During this reaction alkyl-N-formyl alaninate as side product is produced. In the process according to present claims 1 to 8 a dialkyloxalate is used as reactant and the presence of an alkanol is excluded.

D1 discloses the reaction of an amino acid (alanine being mentioned) with a carboxylic acid ester, whereby oxalic acid dialkylesters are not disclosed nor mentioned. This reaction of D1 is carried out in the presence of equimolar amounts of an organic base. In the process according to present claims 1 to 8 dialkyl oxalate is used as reactant and the presence of an added base is excluded.

The subject matter of present claims 1 to 8 is thus novel over said prior art (PCT Article 33.2).

The process of present claim 1 proceeds via the appropriate N-alkoxaly-alanine which is prepared in situ as intermediate of this process.

The process of present claim 9 which is directed to the preparation of N-alkoxaly-alanine differs from the process of D2 by the fact that the product of the claimed process is N-alkoxalyl-alanine whereas D2 discloses the preparation of N-alkoxalyl-alaninates in the presence of an alkanol.

The process of present claim 9 differs from the process of D1 by the fact that D1 does not mention the preparation of N-alkoxalyl-alanine nor the use of a dialkyloxalate as educt nor the given reaction conditions.

The subject matter of present claim 9 is thus novel over said prior art (PCT Article 33.2).

**INTERNATIONAL PRELIMINARY
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(SEPARATE SHEET)**

International application No.
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The compounds of present claim 10 is not disclosed in any of the prior art documents D1 or D2.

The subject matter of present claims ¹⁰ is thus novel over said prior art (PCT Article 33.2).

II. In view of D2 and the prior art cited on pages 1 and 2 of the description the underlying problem can be defined by the provision of a process where the formation of salts is suppressed and where the formation of the alkyl-N-formyl alaninate as side product is suppressed as well.

This problem has been solved as shown by the examples by the use of a dialkyloxalate as reactant under non-acidic conditions.

Neither D2 nor D1 addresses the problem of formation of salts or of alkyl-N-formyl alaninate as side product. There is thus no hint in any of these prior art documents to be found leading to the process of present claims 1 to 8.

The process of present claim 9 is directed to the preparation and isolation of the N-alkoxaly-alanine intermediate. There is no suggestion nor hint to be found in D1 or D2 leading to the specific reaction parameters given in claim 9.

The subject matter of present claims 1 to 9 is thus considered to be based on an inventive step (PCT Article 33.3).

III. Although novelty of present claim 10 is given an indication of problem being solved by the provision of the compound of present claim 10 is missing.

In the absence of a problem which has been solved by the provision of the compound of present claim 10 no inventive step can be acknowledged.

The subject matter of present claim 10 is thus considered not to be based on an inventive step (PCT Article 33.3).

IV. Industrial applicability of present claims 1 to 10 is given (PCT Article 33.4).

V. The description is not in line with the claims on file (Article 6 PCT).

Claims

1. A process for the manufacture of alkyl N-alkoxalyl-alanates, alkylO-CO-CO-NH-CH(CH₃)-CO-Oalkyl, which comprises reacting alanine with a dialkyl oxalate under substantially non-acidic conditions, the reaction being carried out without the presence of an added base or added alkanol.
2. A process according to claim 1, wherein the dialkyl oxalate is a di(C₁₋₈-alkyl) oxalate.
3. A process according to claim 2, wherein the di(C₁₋₈-alkyl) oxalate is a di(C₁₋₄-alkyl) oxalate.
4. A process according to any one of claims 1 to 3, wherein the molar ratio of alanine to dialkyl oxalate is from 1 : 2 to 1 : 10.
5. A process according to claim 4, wherein the molar ratio of alanine to dialkyl oxalate is from 1 : 3 to 1 : 6.
6. A process according to any one of claims 1 to 5, wherein the reaction is carried out at a temperature from 120°C to 200°C.
7. A process according to claim 6, wherein the reaction is carried out at a temperature from 135°C to 160°C.
8. A process according to any one of claims 1 to 7, wherein the reaction is carried out in such a way as to ensure that as much as possible of the alkanol produced during the reaction remains in the reaction system either by carrying out the reaction under atmospheric pressure with cooling of the vapour phase of the reaction mixture to promote the return of the alkanol into the reaction system, or by carrying out the reaction at elevated pressure in a closed system.
9. A process for the manufacture of N-alkoxalyl-alanine which comprises reacting alanine with a dialkyl oxalate under substantially non-acidic conditions wherein the reaction is carried out under atmospheric pressure in the presence of an organic base by heating the reaction mixture for 4 to 12 hours, preferably for 6 to 10 hours, to a

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temperature below the boiling point of the organic base, which, depending on the employed organic base is from 60°C to 160°C, preferably from 80°C to 120°C, most preferably from 90°C to 110°C, thereafter removing any low boiling organic base from the reaction mixture by distillation and isolating the desired N-alkoxalyl-alanine obtained as 5 the major product.

10. N-Ethoxalyl-alanine of the formula $C_2H_5O-CO-CO-NH-CH(CH_3)-COOH$.
